Federal Register
Vol. 48, No. 132
Friday, July 8, 1983

Presidential Documents

Title 3—

The President

Executive Order 12430 of July 6, 1983

Reports of Identical Bids

By the authority vested in me as President by the Constitution and statutes of the United States of America, and in order to eliminate an agency reporting requirement which has proved ineffective and which consumes resources that could be employed in a more effective manner to prevent antitrust violations, Executive Order No. 10936, of April 24, 1961, is hereby revoked.

Ronald Reagan

THE WHITE HOUSE,
July 6, 1983.

[FR Doc. 83-18672
Filed 7-7-83; 11:47 am]
Billing code 3195-01-M

Rules and Regulations

Federal Register
Vol. 48, No. 132
Friday, July 8, 1983

DEPARTMENT OF AGRICULTURE

Agricultural Stabilization and Conservation Service

7 CFR Part 725

[Amdt. 4]

Flue-Cured Tobacco; 1982–83 Average Market Price and 1983–84 Penalty Rate

AGENCY: Agricultural Stabilization and Conservation Service, USDA.

ACTION: Final rule.

SUMMARY: This rule sets forth the average market price received by producers of flue-cured tobacco for the 1982–83 marketing year and the penalty rate for excess tobacco for the 1983–84 marketing year for such kind of tobacco. As required by section 314 of the Agricultural Adjustment Act of 1938, as amended, marketing quota penalties are assessed at the rate of 75 percent of the previous year's average market price.

EFFECTIVE DATE: July 8, 1983.

FOR FURTHER INFORMATION CONTACT: Thomas R. Burgess, Agricultural Program Specialist, Tobacco and Peanuts Division, USDA–ASCS, P.O. Box 2415, Washington, D.C. 20013 (202) 447–2715. A Regulatory Impact Analysis has not been prepared since the effect of this final rule is primarily administrative.

SUPPLEMENTARY INFORMATION: This final rule has been reviewed under USDA procedures established in accordance with Executive Order 12291, and Secretary's Memorandum 1512–1 and has been classified "not major." It has been determined that this rule will not result in: (1) An annual effect on the economy of $100 million or more; (2) a major increase in costs or prices for consumers, individual industries, Federal, State or local government agencies, or geographic regions; or (3) significant adverse effects on competition, employment, investment, productivity, innovation, or the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

The title and number of the Federal Assistance Program to which this rule applies are: Title: Commodity Loan and Purchases; Number: 10.051, as set forth in the Catalog of Federal Domestic Assistance.

It has been determined that the Regulatory Flexibility Act is not applicable to this rule since the Agricultural Stabilization and Conservation Service (ASCS) is not required by 5 U.S.C. 553 or any other provision of law to publish a notice of proposed rulemaking with respect to the subject matter of this rule.

Section 314 of the Agricultural Adjustment Act of 1938 provides that marketing quota penalties shall be assessed whenever a kind of tobacco is marketed in excess of the marketing quota for the farm on which such tobacco is produced. The rate of penalty per pound of a kind of tobacco as prescribed by section 314 of the 1938 Act is 75 percent of the previous year's average market price for such tobacco.

Since the 1982–83 average market price producers received for flue-cured tobacco and the rate of penalty reflect only mathematical computations which are required to be made in accordance with a statutory formula, it has been determined that no further public rulemaking is required. Accordingly, this final rule shall become effective upon date of publication in the **Federal Register.**

List of Subjects in 7 CFR Part 725

Marketing quotas, Penalties, Tobacco.

Final Rule

PART 725—[AMENDED]

Accordingly, the regulations at 7 CFR Part 725 are amended by revising § 725.92(b) to read as follows:

§ 725.92 Rate of penalty.

* * * * *

(b)(1) *Average market price.* The average market prices as determined by the Crop Reporting Board for the marketing years specified were:

AVERAGE MARKET PRICE

Marketing year	Cents per pound
1976–77	110.4
1977–78	117.6
1978–79	135.0
1979–80	140.0
1980–81	144.5
1981–82	166.4
1982–83	178.5

(2) *Rate of penalty per pound.* The penalty per pound for marketings of excess tobacco subject to marketing quotas during the marketing years specified shall be:

RATE OF PENALTY

Marketing year	Cents per pound
1977–78	83
1978–79	88
1979–80	101
1980–81	105
1981–82	108
1982–83	125
1983–84	134

(Secs. 301, 313, 314, 317, 372, 375, 52 Stat. 38, as amended, 47 as amended, 48 as amended, 79 Stat. 66, as amended, 52 Stat. 65, as amended, 66, as amended, (7 U.S.C. 1301, 1313, 1314, 1314c, 1372, 1375))

Signed as Washington, D.C. on July 1, 1983.

Everett Rank,

Administrator, Agricultural Stabilization and Conservation Service.

[FR Doc. 83-18606 Filed 7-7-83; 8:45 am]

BILLING CODE 3410-05-M

Agricultural Marketing Service

7 CFR Part 910

[Lemon Reg. 419]

Lemons Grown in California and Arizona; Limitation of Handling

AGENCY: Agricultural Marketing Service, USDA.

ACTION: Final rule.

SUMMARY: This regulation establishes the quantity of fresh California-Arizona lemons that may be shipped to market during the period July 10–16, 1983. Such action is needed to provide for orderly marketing of fresh lemons for the period due to the marketing situation confronting the lemon industry.

EFFECTIVE DATE: July 10, 1983.

FOR FURTHER INFORMATION CONTACT: William J. Doyle, Chief, Fruit Branch, F&V, AMS, USDA, Washington, D.C. 20250, telephone 202-447-5975.

SUPPLEMENTARY INFORMATION: This final rule has been reviewed under Secretary's Memorandum 1512-1 and Executive Order 12291, and has been designated a "non-major" rule. William T. Manley, Deputy Administrator, Agricultural Marketing Service, has certified that this action will not have a significant economic impact on a substantial number of small entities. This action is designed to promote orderly marketing of the California-Arizona lemon crop for the benefit of producers, and will not substantially affect costs for the directly regulated handlers.

This final rule is issued under Marketing Order No. 910, as amended (7 CFR Part 910; 47 FR 50196), regulating the handling of lemons grown in California and Arizona. The order is effective under the Agricultural Agreement Act of 1937, as amended (7 U.S.C. 601-674). The action is based upon recommendations and information submitted by the Lemon Administrative Committee and upon other available information. It is hereby found that this action will tend to effectuate the declared policy of the Act.

This action is consistent with the marketing policy for 1982-83. The marketing policy was recommended by the committee following discussion at a public meeting on July 6, 1982. The committee met again publicly on July 5, 1983, at Los Angeles, California, to consider the current and prospective conditions of supply and demand and recommended a quantity of lemons deemed advisable to be handled during the specified week. The committee reports the demand for lemons is good.

It is further found that it is impracticable and contrary to the public interest to give preliminary notice, engage in public rulemaking, and postpone the effective date until 30 days after publication in the **Federal Register** (5 U.S.C. 553), because of insufficient time between the date when information became available upon which this regulation is based and the effective date necessary to effectuate the declared purposes of the act. Interested persons were given an opportunity to submit information and views on the regulation at an open meeting. It is necessary to effectuate the declared purposes of the act to make these regulatory provisions effective as specifed, and handlers have been apprised of such provisions and the effective time.

List of Subjects in 7 CFR Part 910

Marketing agreements and orders, California, Arizona, Lemons.

PART 910—[AMENDED]

Section 910.719 is added as follows:

§ 910.719 Lemon regulation 419

The quantity of lemons grown in California and Arizona which may be handled during the period July 10, 1983, through July 16, 1983, is established at 350,000 cartons.

(Secs. 1-19, 48 Stat. 31, as amended; 7 U.S.C. 601-674)

Dated: July 7, 1983.

D. S. Kuryloski,

Deputy Director, Fruit and Vegetable Division, Agricultural Marketing Service.

[FR Doc. 83-18673 Filed 7-7-83; 12:05 pm]

BILLING CODE 3410-02-M

SMALL BUSINESS ADMINISTRATION

13 CFR Part 108

Loans to State and Local Development Companies; Eligibility Requirements for Certified Development Companies

AGENCY: Small Business Administration.

ACTION: Correction of final rule.

SUMMARY: This corrects a final rule published in the **Federal Register** on August 10, 1982 (47 FR 34530) concerning eligibility requirements for certified development companies.

EFFECTIVE DATE: July 8, 1983.

FOR FURTHER INFORMATION CONTACT: Wayne Foren, Director, Office of Lender, Relations and Certification, Small Business Administration, 1441 L Street, N.W., Room 720, Washington, D.C. 20416, (202) 653-6416.

SUPPLEMENTARY INFORMATION: On August 10, 1982, SBA published a final rule (47 FR 34530) amending Section 108.503-1. This amendment added a new paragraph (b) "Area of Operation" and recodified and changed existing paragraph (b) "Membership", as paragraph (c).

Inadvertently, existing paragraphs (c) and (d), which should have been recodified as (d) and (e), were omitted from the change as published. This correction will rectify that omission.

Pursuant to authority contained in section 308(c) of the Small Business Investment Act of 1958 (SBI Act), 15 U.S.C. 687, Chapter 1, Part 108 of Title 13, Code of Federal Regulations is being corrected as follows:

List of Subjects in 13 CFR Part 108

Loan programs—business (503 Program)

PART 108—[AMENDED]

In § 108.503-1, paragraphs (d) and (e) are added as follows:

§ 108.503-1 Eligibility requirements.

* * * * *

(d) *Good character and reputation.* A proposed 503 company must possess good character and reputation. Such company will be deemed to possess good character and reputation if all the holders of its voting power and all members of its management possess good character and reputation. Good character and reputation shall be presumed absent if such holders or management are currently incarcerated, on parole or probation following conviction of a serious offense, or when probation or parole is lifted solely for qualification under this program.

(e) *Sole purpose intention.* A 503 company shall operate pursuant to Title V of the Small Business Investment Act (Loans to State and Local Development Companies) and shall not participate in any other SBA program.

(Catalog of Federal Domestic Assistance No. 59.013 State and Local Development Company Loans)

Dated: June 30, 1983.

Heriberto Herrera,

Acting Administrator.

[FR Doc. 83-18507 Filed 7-7-83; 8:45 am]

BILLING CODE 8025-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 73

[Docket No. 83C-0051]

Listing of Color Additives for Coloring Contact Lenses

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the color additive regulations to provide for the safe use of four color additives for coloring contact lenses. This action is a partial response to a petition filed by Custom Tint Laboratories, Inc.

DATES: Effective August 9, 1983; objections by August 8, 1983.

ADDRESS: Written objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm.

4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Rudolph Harris, Bureau of Foods (HFF–334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–472–5690.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of June 17, 1983 (48 FR 27834), FDA announced that a color additive petition (CAP 3C0169) had been filed by Custom Tint Laboratories, Inc., 6020 Six Forks Rd., Raleigh, NC 27609, proposing that the color additive regulations be amended to provide for the safe use of two orange dyes, 6,6'-diethoxy-2,2'-[3*H*,3'*H*]bibenzo[*b*] thiophene-3,3'-dione and dibromodibenzo[*b,def*] chrysene-7,14-dione; a brown dye, 16,23-diehydrodinaphtho[2,3-*a*:2',3'-*i*]naphth[2',3':6,7]indolo[2,3-*c*]carbazole-5,10,15,17,22,24-hexone; a yellow dye, *N,N'*-(9,10-dihydro-9,10-dioxo-1,5-anthracenediyl) bisbenzamide; a blue dye, 7,16-dichloro-6,15-dihydro-5,9,14,18-anthrazinetetrone; and a green dye, 16,17-dimethoxydinaphtho[1,2,3-*cd*:3',2',1'-*lm*]perylene-5,10-dione for coloring contact lenses. The petition was filed under section 706 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 376).

With the passage of the Medical Device Amendments of 1976 (Pub. L. 94–295) to the act, Congress mandated the listing of color additives for use in medical devices where the color additive comes in direct contact with the body for a significant period of time (21 U.S.C. 376 (a)). The use of the six color additives presented in the petition now before the agency is subject to this listing requirement. These color additives are added to contact lenses in such a way that at least some of the color additive will come in contact with the eye when the lenses are worn. In addition, the lenses are intended to be placed in the eye for several hours a day each day for 1 year or more. Thus, the color additives will be in direct contact with the body for a significant period of time.

To establish that the color additives are safe for coloring the contact lenses it manufactures, the petitioner submitted toxicity and analytical data. The data reveal that the amount of these color additives that can be added to contact lenses is self-limiting because tinting above a certain intensity will result in a loss of visibility and a substantial and unacceptable distortion of color for the wearer. If each of a pair of lenses contains the amount of color additive necessary to achieve the maximum acceptable intensity, and all of the color additive migrates from the lenses to the eye over the lifetime of the lenses (1 year), the maximum exposure to the color additive from the pair of lenses will not exceed 20 nanograms per day (ng/day).

FDA has evaluated the toxicity data, which include the results of in vitro cytotoxicity tests of the color additives at many times the maximum use level in lenses and of primary ocular irritation studies in rabbits with saline extracts of the tinted lens materials. Based upon the results of these studies, FDA finds that it can conclude to a reasonable certainty that no harm will result from the petitioned use of 16,23-dihydrodinaphtho[2,3-*a*:2',3'-*i*]naphth[2',3':6,7]indolo[2,3-*c*]*carbazole-5,10,15,17,22,24-hexone; N,N'*-(9,10-dihydro-9,10-dioxo-1,5-anthracenediyl) bisbenzamide; 7,16-dichloro-6,15-dihydro-5,9,14,18-anthrazinetetrone; and 16,17-dimethoxydinaphtho[1,2,3-*cd*:3',2',1'-*lm*]perylene-5,10-dione. To ensure the safe use of these substances, FDA is adopting regulations that state that these substances may be used to color contact lenses in amounts not to exceed the minimum reasonably required to accomplish the intended coloring effect.

FDA will issue shortly a separate order for 6,6'-diethoxy-2,2'-[3*H*,3'*H*] bibenzo[*b*]thiophene-3,3'-dione and is deferring final action on the color additive dibromodibenzo [*b,def*]chrysene-7,14-dione pending receipt and evaluation of additional studies. Use of these two color additives will continue for the short period of time necessary to complete action on them under an investigational device exemption previously granted by FDA.

Based on its consideration of the factors listed in § 71.20(b) (21 CFR 71.20(b)), the agency concludes that certification of the four color additives listed by this final rule is not necessary for the protection of the public health.

In accordance with § 71.15(a) (21 CFR 71.15(a)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the use of these color additives in contact lenses are available for inspection at the Bureau of Foods (address above) by appointment with the information contact person listed above. As provided in § 71.15(b), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting this finding may be seen in the Dockets Management Branch (address above), between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 73

Color additives, Color additives exempt from certification, Color diluents, Cosmetics, Drugs, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 701(e), 706, 70 Stat. 919 as amended, 74 Stat. 399–407 as amended (21 U.S.C. 371(e), 376) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), Part 73 is amended in Subpart D by adding new §§ 73.3117 through 73.3120, to read as follows:

PART 73—LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION

§ 73.3117 16,23-Dihydrodinaphtho[2,3-a:2',3'-i] naphth [2',3':6,7] indolo [2,3-c] carbazole-5,10,15,17,22,24-hexone.

(a) *Identity.* The color additive is 16,23-dihydrodinaphtho [2,3- *a*:2',3'-*i*] napth [2',3':6,7] indolo [2, 3-*c*] carbazole-5,10, 15,17,22,24-hexone (CAS Reg. No. 2475–33–4), Colour Index No. 70800.

(b) *Uses and restrictions.* (1) The substance listed in paragraph (a) of this section may be used as a color additive in contact lenses in amounts not to exceed the minimum reasonably required to accomplish the intended coloring effect.

(2) Authorization for this use shall not be construed as waiving any of the requirements of sections 510(k), 515, and 520(g) of the Federal Food, Drug, and Cosmetic Act with respect to the contact lens in which the color additive is used.

(c) *Labeling.* The label of the color additive shall conform to the requirements of § 70.25 of this chapter.

(d) *Exemption from certification.* Certification of this color additive is not necessary for the protection of the public health, and therefore the color additive is exempt from the certification requirements of section 706(c) of the act.

§ 73.3118 N,N'-(9,10-Dihydro-9,10-dioxo-1,5-anthracenediyl) bisbenzamide.

(a) *Identity.* The color additive is *N,N'*-(9,10-dihydro-9,10-dioxo-1,5-anthracenediyl) bisbenzamide (CAS Reg. No. 82–18–8), Colour Index No. 61725.

(b) *Uses and restrictions.* (1) The substance listed in paragraph (a) of this section may be used as a color additive

in contact lenses in amounts not to exceed the minimum reasonably required to accomplish the intended coloring effect.

(2) Authorization for this use shall not be construed as waiving any of the requirements of sections 510(k), 515, and 520(g) of the Federal Food, Drug, and Cosmetic Act with respect to the contact lens in which the color additive is used.

(c) *Labeling.* The label of the color additive shall conform to the requirements of § 70.25 of this chapter.

(d) *Exemption from certification.* Certification of this color additive is not necessary for the protection of the public health, and therefore the color additive is exempt from the certification requirements of section 706(c) of the act.

§ 73.3119 7,16-Dichloro-6,15-dihydro-5,9,14,18-anthrazinetetrone.

(a) *Identity.* The color additive is 7,16-dichloro-6,15-dihydro-5,9,14,18-anthrazinetetrone (CAS Reg. No. 130-20-1), Colour Index No. 69825.

(b) *Uses and restrictions.* (1) The substance listed in paragraph (a) of this section may be used as a color additive in contact lenses in amounts not to exceed the minimum reasonably required to accomplish the intended coloring effect.

(2) Authorization for this use shall not be construed as waiving any of the requirements of sections 510(k), 515, and 520(g) of the Federal Food, Drug, and Cosmetic Act with respect to the contact lens in which the color additive is used.

(c) *Labeling.* The label of the color additive shall conform to the requirements of § 70.25 of this chapter.

(d) *Exemption from certification.* Certification of this color additive is not necessary for the protection of the public health, and therefore the color additive is exempt from the certification requirements of section 706(c) of the act.

§ 73.3120 16,17-Dimethoxydinaphtho [1,2,3-cd:3',2',1'-lm]perylene-5,10-dione.

(a) *Identity.* The color additive is 16,17-dimethoydinaphtho[1,2,3,-*cd*:3',2',1'-*lm*]perylene-5,10-dione (CAS Reg. No. 128-58-5), Colour Index No. 59825.

(b) *Uses and restrictions.* (1) The substance listed in paragraph (a) of this section may be used as a color additive in contact lenses in amounts not to exceed the minimum reasonably required to accomplish the intended coloring effect.

(2) Authorization for this use shall not be construed as waiving any of the requirements of sections 510(k), 515, and 520(g) of the Federal Food, Drug, and Cosmetic Act with respect to the contact lens in which the color additive is used.

(c) *Labeling.* The label of the color additive shall conform to the requirements of § 70.25 of this chapter.

(d) *Exemption from certification.* Certification of this color additive is not necessary for the protection of the public health, and therefore the color additive is exempt from the certification requirements of section 706(c) of the act.

Any person who will be adversely affected by the foregoing regulation may at any time on or before August 8, 1983 file with the Dockets Management Branch (address above) written objections thereto. Objections shall show wherein the person filing will be adversely affected by the regulation, specify with particularity the provisions of the regulation deemed objectionable, and state the grounds for the objections. Objections shall be filed in accordance with the requirements of 21 CFR 71.30. If a hearing is requested, the objections shall state the issues for the hearing and shall be supported by grounds factually and legally sufficient to justify the relief sought, and shall include a detailed description and analysis of the factual information intended to be presented in support of the objections in the event that a hearing is held. Three copies of all documents shall be filed and shall be identified with the docket number found in brackets in the heading of this document. Any objections received may be seen in the Dockets Management Branch, between 9 a.m. and 4 p.m., Monday through Friday.

Effective date. This regulation shall become effective August 9, 1983 except as to any provisions that may be stayed by the filing of proper objections. Notice of the filing of objections or lack thereof will be announced by publication in the **Federal Register.**

(Secs. 701(e), 706, 70 Stat. 919, as amended, 74 Stat. 399-407 (21 U.S.C. 371(e), 376))

Dated: July 1, 1983.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 83-18370 Filed 7-7-83; 8:45 am]

BILLING CODE 4160-01-M

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21 CFR Part 172

[Docket No. 82F-0305]

Food Additives Permitted for Direct Addition to Food for Human Consumption; Aspartame

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of aspartame in carbonated beverages and carbonated beverage syrup bases. The action responds to a petition filed by G. D. Searle & Co.

DATES: Effective July 8, 1983; objections by August 8, 1983.

ADDRESS: Written objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Anthony P. Brunetti, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St., SW., Washington, D.C. 20204, 202-472-5690.

SUPPLEMENTARY INFORMATION:

I. Introduction

Aspartame, the methyl ester of a digestible dipeptide, with a nutritive value of four calories per gram, was first approved as a sugar substitute for table use, and for use in certain dry food applications as a sweetener and flavor enhancer on July 26, 1974 (39 FR 27317; correction published September 26, 1974 (39 FR 34520)). The approval responded to a petition from G. D. Searle & Co. and the regulation became codified in 21 CFR 172.804 (formerly 21 CFR 121.1258).

Formal objections to this regulation, based on safety concerns arising from toxic effects of certain amino acids in animals, resulted in the establishment of a Public Board of Inquiry (the Board) to investigate the safety questions. A comprehensive audit of the authenticity of selected toxicological studies on aspartame was also undertaken, and the regulation authorizing the marketing of aspartame was stayed pending the findings of these inquiries (40 FR 56907; December 5, 1975). In the **Federal Register** of July 24, 1981 (46 FR 38285; correction published September 18, 1981 (46 FR 46394)), the Commissioner of Food and Drugs reviewed in detail the contested aspects of aspartame's safety and issued his final decision on Searle's petition for the food additive use of aspartame ("Commissioner's decision"). The Commissioner's decision concluded that aspartame had been shown to be safe under section 409 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348), and vacated the stay of the original regulation, effective October 22, 1981 (46 FR 50947; October 16, 1981).

In a notice published in the Federal Register of October 15, 1982 (47 FR 46140), FDA announced that a petition (FAP 2A3661) had been filed by the Searle Research and Development Division of G. D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077, proposing that § 172.804 *Aspartame* be

amended to provide for the additional safe use of aspartame (1-methyl *N*-L-α-aspartyl-L-phenylalanine) as a sweetener in carbonated beverages.

II. Petition for Use in Carbonated Beverages

The proposed use of aspartame in carbonated beverages required the current petition to address the new issue of the stability of aspartame in a liquid medium. In addition, the petition had to address the issue of the dietary exposure to aspartame resulting from its use in carbonated beverages, as well as from other regulated uses. Safety data, in the form of clinical studies with various human subpopulations, were also provided to support the safe use of aspartame at the highest estimated exposure levels. These issues are discussed below.

A. Stability of Aspartame in Beverages

Studies on aspartame's stability in carbonated beverages and syrup concentrates were provided by Searle in the current petition to demonstrate the safety and functionality of the sweetener in carbonated beverages during typical storage periods (up to 52 weeks), and over a range of temperatures 5° to 55° C (41° to 131° F). These stability data were submitted under section 409(b)(2)(C) of the act which requires that a food additive petition contain data bearing on the physical or technical effect the additive is intended to produce. Sensitive chromatographic analyical techniques were used to identify and quantify aspartame and its decomposition products in the aged carbonated beverage preparations. Taste panel tests also verified that taste characteristics were retained for typical shelf-life periods. For example, levels of aspartame remaining in carbonated beverages stored for 8 weeks at 20° C (68° F) were shown to be between 84 and 89 percent of the original amount. The lost aspartame is degraded to diketopiperazine (DKP) and its component amino acids, aspartic acid, phenylalanine, plus aspartyl-1-phenylalanine (the deesterified dipeptide), and methanol. The DKP formed was 3 to 4 percent of the added aspartame. Approximately one-third of the decomposition products were in the form of DKP, a result which was shown to be relatively consistent for four flavors of carbonated beverages as well as for the syrup concentrates. At average aspartame use levels, 67 milligrams (mg) per 100 milliliters (mL) of carbonated beverage, the level of DKP formed was demonstrated to be approximately 2 mg/100 mL under these conditions. Storage at 5° C (41° F) for 52 weeks results in residual aspartame levels similar to the above. After 8 weeks at 5° C, aspartame levels were 90 percent of the amounts added.

Storage tests at 30° C (86° F) for 8 weeks resulted in 62 percent of the added aspartame remaining in a cola-type beverage, with 12 percent of the residue in the form of DKP. At temperatures above 30° C the stability drops off markedly. The petition shows that storage at 40° C (104° F) and 55° C (131° F) results in less than one-half of the added aspartame remaining after 9 weeks and 3 to 4 weeks, respectively. The agency believes, however, that storage at these times and temperatures can be avoided by attention to handling and distribution. More important, although this lack of stability might result in a marginally acceptable product, it would not lead to an unsafe product. Any concern over possible toxic effects from DKP has been eliminated as a result of long-term animal studies conducted using DKP itself as the test compound. These studies are discussed below in greater detail under "Safety Issues."

B. Consumption Levels

The additional use of aspartame in carbonated beverages is expected to increase the projected average daily consumption of the sweetener. Safety issues relating consumption levels of the sweetener to potential toxic effects from its component amino acid have been comprehensively reviewed in the Commissioner's final decision of July 24, 1981 (46 FR 38285). In the safety analysis of consumption levels described therein, estimates of the maximum possible daily intake of aspartame were computed by several methods (46 FR 38290). Significantly, these aspartame consumption estimates included calculations based on: (a) Substitution of aspartame for all sucrose in the diet of an average 60-kilogram (kg) individual (8.3 mg/kg body weight of aspartame per day), or substitution of aspartame for all dietary carbohydrate (25 mg/kg body weight per day); and (b) market survey data of actual dietary records for foods which could contain aspartame (data compiled by Market Research Corp. of America (MRCA)). The estimates based on the MRCA survey covered two groups of products: "Group A" products were those which are now approved for addition of aspartame (21 CFR 172.804); and "Group B" products include seven additional food categories for which aspartame has marketing potential, including carbonated beverages. The Commissioner thus considered use of aspartame in carbonated beverages in estimating its potential consumption.

For the product Groups A and B combined, the consumer group with the highest intake (young children, ages 2 to 5) had a calculated mean potential exposure of 11.1 mg/kg body weight per day, and a corresponding 90th percentile value of 25.0 mg/kg. Members of the Board, as well as the Commissioner, used an intake value of 34 mg/kg per day in their analysis of possible risk. This figure was the highest obtained from any estimate of potential consumption and exceeds the 99th percentile consumption (25 mg/kg) for all age groups combined from the MRCA survey. Subsequent safety calculations relating to the maximum risk from elevations in blood plasma levels of aspartame's component amino acids were referenced to this "loading dose" of aspartame consumption (46 FR 38304). The corresponding minimum elevation in plasma levels of amino acids that could be suspected of being neurotoxic was taken to be 100 micromoles per deciliter (dL), the cautiously estimated "toxic threshold" value adopted for human risk assessment purposes (46 FR 38291).

Referring to the projected maximum aspartame consumption estimate of 34 mg/kg per day and the threshold plasma level, the Commissioner concluded that all the evidence available established that aspartame intake from the maximum projected consumption of aspartame, which included beverage use, was "far, far below any level even suspected of being toxic" (46 FR 38303). After the Commissioner's decision was issued, the MRCA survey was updated with more recent data. Present consumption estimates based on the agency's analysis of the most recent MRCA survey compilations for products approved for aspartame use (and carbonated beverages) yield values comparable to those found by the Commissioner when aspartame was approved: mean intake in the 2- to 4-year age group is 12 mg/kg, and 24 mg/kg for the 90th percentile eaters in this group. The 99th percentile estimate for all age groups combined is 25 mg/kg. Current estimates of aspartame consumption are consistent with previous estimates and, therefore, the agency concludes that the maximum projected consumption of aspartame, including the use of aspartame in

carbonated beverages, is not regarded as being of toxicological concern.

C. Comments

FDA has received three comments in response to the October 15, 1982 notice of filing for Searle's new petition proposing the additional use of aspartame as a sweetener in carbonated beverages. These comments are discussed immediately below and the agency's response to them is set forth in Part III, "Safety Issues."

The first comment raised the following three issues: (1) Whether aspartame is sufficiently stable for liquid beverage use, (2) whether the resulting increase in consumption of aspartame and its component amino acids, phenylalanine and aspartic acid, would result in blood levels of amino acids which exceed previously "implied margins of safety," and (3) whether phenylalanine and aspartic acid have an adverse effect on neurotransmitter activity at concentrations and durations of exposure well below those involved in classical toxicological testing.

The second comment questioned the safety of aspartame for both carbonated beverage use and the currently approved uses. The letter contained an anonymous report (the anonymous report), authored by a "concerned scientist and citizen," with the stated purpose of reviewing aspartame's "unresolved" safety issues. No significant data or literature references were presented in the anonymous report other than a reference to unpublished results from a reproductive study with DKP. The safety issues relative to the use of aspartame, which the anonymous report identified as "unresolved" or "new areas of concern," were as follows: Risks to the general public, including brain cancer, possible toxic reaction products, nitrosation potential of aspartame and/or DKP; risks to children, including brain damage, phenylketonuria (PKU), and methyl alcohol; risks to the fetus and pregnant women, including mental retardation and induced resorptions; and risks to individuals already physiologically compromised, including persons with liver disease, diabetics, and the geriatric population.

A third comment raised a concern about possible adverse behavioral effects resulting from a diet consisting of high levels of aspartame in combination with high levels of carbohydrate. The comment argued that such an unusual dietary pattern, particularly after an overnight fasting period, could elevate plasma-phenylalanine levels while simultaneously depressing the concentration of other neutral amino acids in the blood. The plasma concentration ratio of phenylalanine to the sum of the other neutral amino acids is generally believed to be indicative of the corresponding brain levels of phenylalanine.

The comment claimed that the reported elevations in the plasma-phenylalanine ratio due to the unusual dietary regimen would lead to elevated brain levels of phenylalanine which may affect brain enzymes influencing the production of neurotransmitters in the brain, and this change in neurotransmitter production may ultimately lead to behavioral effects. The comment acknowledged, however, that any transient perturbations in brain amino acid metabolism caused by dietary exposure, such as the experimentally administered combination of high aspartame and high sucrose, are unlikely to lead to neurotoxicity. The comment also noted that the observed elevations in the plasma-phenylalanine ratio are much less than those which accompany phenylketonuria. The comment included a summary of results from preliminary experiments with five human subjects. These limited data showed an expected increase in the plasma-phenylalanine ratio, although the agency has not had access to the complete experimental data.

The agency believes that the majority of the safety questions posed in these comments are the same questions that were examined and evaluated previously by the agency and the Board. The Commissioner's final decision which discusses these issues in detail was published in the **Federal Register** of July 24, 1981 (46 FR 38284) and transcripts of all of the expert testimony before the Board, all of the scientific data, and agency memoranda and correspondence associated with these past safety decisions on aspartame are part of the public record available for review at the Dockets Management Branch (address above). Because of the availability of this record, the agency concludes that it is not necessary to respond again in detail to these issues. The agency has, however, responded briefly to these comments below, using references where appropriate.

III. Safety Issues

A. Brain Damage

The Commissioner's decision approving the food additive petition for aspartame found that there was no reasonable expectation that aspartame ingestion could influence either of two distinct types of brain damage. Specifically, the Commissioner found that there was a reasonable certainty that aspartame: (1) Does not cause brain tumors in rats and (2) does not pose a risk of contributing to mental retardation, brain lesions, or undesirable effects on neuroendocrine regulatory systems in humans.

The comments on the use of aspartame in carbonated beverages raised these same issues. The comments argued that the Commissioner's decision was incorrect regarding aspartame's potential for causing brain tumors, relying on the Board's disagreement with the Commissioner on this issue. The comments further argued that, in requiring post-market surveillance to confirm aspartame consumption levels, the agency had indirectly admitted that there is a potential risk of brain damage of the type described in item (2) above.

The comments did not, however, present any significant new information concerning the probability of toxic responses in humans due to the ingestion of aspartame.

1. *Aspartame's Potential for Causing Brain Tumors.* Interpretation of the results of the chronic rat feeding studies designed to determine aspartame's potential for causing brain tumors was one of the major scientific issues before the Board, and consequently one of the most comprehensively deliberated issues relative to aspartame's safety. The Board found that the results of these tests were not sufficiently conclusive and recommended that approval of aspartame be withheld pending results from further oncogenic studies with the additive. The Commissioner disagreed with the Board's findings and, as noted above, concluded that there was a reasonable certainty that aspartame does not cause brain tumors in rats. One of the comments contends that the Board's findings, rather than the Commissioner's, were correct. The comment did not, however, submit any new data on this issue.

An account of the record with regard to the positions of the Board and the Commissioner on the brain tumor studies, and a presentation of the reasons for the Commissioner's exceptions to the Board's findings, have been clearly stated in the Commissioner's final decision (46 FR 38295). This decision is fully supported by the record which included not only the three chronic studies before the Board, but also negative results observed in subsequent animal studies not available to the Board. Furthermore, the comments fail to acknowledge that two of the three members of the Board later concurred with the Commissioner's rebuttal of their evaluation, even though

the concurrence of these Board members is expressed in the same published article (*Science*, August 28, 1981) upon which the comment relies.

The administrative record shows that the regulatory approval of aspartame is supported by a complete series of toxicological tests in animals. These studies have been thoroughly reviewed by FDA scientists. Based on that review and for the reasons stated in the Commissioner's decision, the agency reaffirms the conclusion that there is a reasonable certainty that aspartame does not cause brain tumors in rats.

2. *Aspartame's Potential for Causing Mental Retardation, Brain Lesions, and Other Effects.* The major concerns about toxic effects from aspartame consumption are the possibility of adverse responses to its component amino acids, phenylalanine and aspartate. Because these amino acids are also constituents of normal dietary protein, any risk from aspartame ingestion must be considered in the context of the resulting increase in exposure to these amino acids compared with the exposure from the normal diet. The potential toxicity of these amino acids is discussed below.

a. *Aspartate.* High blood levels of aspartic and glutamic acids have been associated with focal brain lesions in animals after parenteral (non-dietary) administration of large doses of aspartate or glutamate (46 FR 38291). One of the comments on this issue contended that, in requiring postmarket surveillance of aspartame, the Commissioner indirectly admitted aspartame's potential to cause brain damage.

This contention is incorrect. Prior to the approval of a food additive petition, the agency is required to find that there is a reasonable certainty of no harm from the proposed use of a substance, as judged by competent scientists (21 CFR 170.3(i)). The Commissioner found that the evidence in support of aspartame's safety met this standard. The postmarketing survey was required to ensure the accuracy of estimates of the consumption of aspartame, not because of any doubts about its safety.

In determining the potential risk of aspartic and glutamic acids, the Commissioner and members of the Board did accept the assumption that a combined plasma level of 100 micromoles/dL of the amino acids glutamate and aspartate may be toxic in humans. It must be understood, however, that this assumption was made to permit potential risk comparisons to be made under assumed worst case exposure conditions. There is no evidence establishing that these levels are toxic in healthy humans, nor has it been shown that amino acid levels can attain this "threshold" concentration by ingestion of large doses of aspartame.

Searle's petition for carbonated beverage use of aspartame specifically addressed the issue of the potential glutamate and aspartate toxcity through the submission of new clinical safety studies. In these studies, the effects on amino acid blood levels resulting from the acute administration of high doses of aspartame were observed on different human subpopulations: normal adults, adolescents and children, diabetics, lactating mothers, infants, and obese and glutamate-sensitive individuals. These studies demonstrated that, when ingested aspartame doses are several multiples of the highest projected daily intake levels, only one-tenth, i.e., 10 micromoles/dL, of the conservatively derived toxic threshold value noted above is attained in humans. This margin of safety is considerable and adds additional support to the Commissioner's conclusion that the proposed use of aspartame, either alone or in combination with glutamate, will not cause focal brain lesions under conditions of use that include use of aspartame to sweeten carbonated beverages (46 FR 38294).

b. *Phenylalanine.* Sustained elevations of plasma-phenylalanine, resulting from the genetic disorder known as phenylketonuria (PKU), can lead to mental retardation in those infants who are homozygous for the gene coding for the deficient form of the enzyme, phenylalanine hydroxylase. One comment expressed concern that the proposed use of aspartame would increase the incidence of the particular form of mental retardation associated with sustained elevations of plasma-phenylalanine levels. Both the Board and the Commissioner agreed that such an increase in mental retardation would not be expected (46 FR 38290–91). Because no significant new evidence has been submitted concerning this issue, the agency has decided that the Commissioner's conclusion was correct for the reasons stated in his decision (*id.*).

Another comment expressed concern that extreme dietary patterns (aspartame and carbohydrate) may enhance the potential adverse effects of elevated plasma-phenylalanine levels by causing an increase in the concentration of phenylalanine and a concomitant decrease in the sum of the concentrations of other neutral amino acids in the blood. Resulting increases in the ratio of these quantities is postulated in the comment to be proportional to increased phenylalanine levels in the brain.

The comment provided limited details of experimental observations made on 5 human subjects. The subjects had received large doses of aspartame (about 1 gram (g)) in 2 quarts of beverage followed by a confection containing 200 g of sucrose, administered after overnight fasting. Increases were measured in the plasma phenylalanine ratio. It is difficult, however, if not impossible, to interpret the significance of the experiments in terms of normal eating habits and in the absence of a control experiment feeding only aspartame.

The comment maintains that toxic effects would not be anticipated from transient increases in the plasma phenylalanine ratio, but the concurrent changes in neurotransmitter activity due to expected changes in brain metabolism may be sufficient to affect human behavior, performance, and subjective feelings. The agency believes that the comment's conclusion regarding potential phenylalanine induced changes in neurotransmitter function appear to be unwarranted extrapolations. Even though elevated plasma amino acid ratios may produce similar elevations of the amino acid in the brain as claimed, recent detailed studies in the rat by Fernstrom, et. al., the best evidence submitted to FDA thus far, does not support the view that neurotransmitter activity is altered (Ref. 1). In one study, serum and brain levels of amino acids were measured in rats given up to 200 mg/kg of aspartame by gavage. The results of this work indicate that the elevations in phenylalanine plasma ratios and brain levels are not sufficient to influence either the levels or the rate of turnover of catecholamine or indoleamine neurotransmitters in the brain of the rat. Thus, perturbations in phenylalanine plasma ratios greater than those caused by the extreme dietary manipulation in the human study failed to produce the effects predicted by the comment on the levels of monoamines which are acepted indicators of neurotransmitter function.

To test the aspartame-carbohydrate dietary hypothesis, the person submitting these comments recently repeated the work of Fernstrom, *et al.* In addition to the 200 mg/kg of aspartame used by Fernstrom, fasted rats were first fed 3 g/kg of carbohydrate (as glucose). The agency has reviewed the results of these studies. The brain levels of the neurotransmitter serotonin and its metabolite 5-hydroxyindole acetic acid were assayed. In the rats fed the aspartame/carbohydrate diet, the levels

of these substances linked to serotenergic neurotransmitter function were essentially the same as those of the control group.

In conclusion, the agency finds that the data supplied with this comment do not provide support for its hypothesis that the ingestion of aspartame and carbohydrate will alter the brain levels of neurotransmitters, and thereby produce behavioral modification.

Further support for the safety of aspartame with respect to its contribution to additional dietary phenylalanine comes from previously submitted studies with infant monkeys (macaques) (Ref. 2). These animals were fed up to 3,000 mg/kg of aspartame or 1,650 mg/kg of phenlalanine in a liquid formula for 9 months. Postprandial blood levels of phenylalanine ranged from 180 to 300 micromoles/dL. Although these infant macaques were exposed to extremely high levels of phenylalanine (with phenylalanine-plasma ratios well in excess of those in the human study), the animals grew and developed normally. In addition, none of the treated or control animals showed electroencephalographic abnormalities or behavioral seizures.

Subsequent to the withdrawal of the macaques from the high aspartame/phenylalanine diets, the animals were also subjected to behavioral testing consisting of a series of a standardized primate tests. No differences were observed in the test scores between any of the treatment groups. These results support the conclusion that prolonged exposure to extremely high plasma levels of phenylalanine produced no long-term or irreversible changes in the physical or mental development in the primates.

The petitioner has also submitted studies in which aspartame has been administered to humans in acute doses of 34, 50, 100, and 150 mg/kg. No evidence of effects on mood or mental performance was observed (Ref. 3). Nausea was reported in subjects following ingestion of 200 mg/kg of aspartame, a result attributed to the extreme sweetness of aspartame. (The sweetness of 200 mg/kg of aspartame is comparable to eating 5.5 pounds of sucrose in a single serving.) Thus, the agency concludes, based on a review of all the relevant scientific data available, that the ingestion of aspartame, either alone or in combination with high levels of carbohydrate, will not result in behavorial modification even under the dietary extremes cited in the comment.

B. Decomposition and Reaction Products

1. *Diketopiperazine (DKP).* Aspartame is known to decompose at elevated temperatures, and in solution it decomposes at a rate that is dependent on the pH of the solution and its temperature. The decomposition products consist primarily of its component amino acids (phenylalanine and aspartic acid), methanol, and its DKP derivative. Of these products, only DKP is an uncommon constituent of foods. Amino acids are the subunits of all proteins, and methanol is a common metabolite of methyl esters found in a variety of foods. The original aspartame regulation, allowing use in dry foods, relied on data in the petition and the related master file demonstrating that the additive was sufficiently stable to be efficacious as a sweetener in such products. In these dry food uses DKP normally comprises less than two percent of added aspartame.

The comments objecting to the use of aspartame in liquid foods expressed concern about the toxicity of its decomposition products, particularly DKP. Subsequent to the original approval (1974) of aspartame for use in dry foods, the petitioner completed a series of toxicological tests on DKP. These studies included reproductive, mutagenic, and chronic bioassays in two rodent species. After evaluating these studies, the agency derived a no effect level of 3,000 mg/kg body weight to DKP. Based on these results, the acceptable daily intake of DKP exceeds any dietary exposure that is likely to result from aspartame consumption at the 99 percent level (25 mg/kg), even if total conversion to DKP is assumed.

One comment also contended that recent animal studies with DKP, conducted at the University of Louvain in Belgium by Professor Lederer and coworkers, have shown DKP to have adverse effects on fetal development. Although the agency has not had access to the complete experimental data resulting from this work, correspondence from Professor Lederer, as well as a summary report of the investigation, discloses that the authors conclude that no teratogenic effects were observed. Contrary to the implication made in the anonymous report submitted with one of the comments, no decrease in the number of implants or increase in the number of resorptions were observed which could be attributed in a dose-related manner to the maternal administration of DKP. Decreases in the number of implants, seen at the 1 percent DKP level relative to control animals, were not observed in the corresponding group fed at the highest level, 3 percent dietary DKP for 20 days of gestation. Consequently, the agency finds that its conclusion on the safety of DKP with regard to potential embryotoxicity need not be reexamined. Furthermore, the only dose-related effect observed in Lederer's study was a slight reduction in embryo (fetal) weights at the highest dose level of DKP. Prior to the original approval of aspartame, the agency also reviewed a series of four reproductive studies with DKP and DKP/aspartame mixtures. Two of these studies were in the rabbit and two studies were in the rat. No embryotoxic or teratogenic effects were demonstrated in these studies. In addition, there was no evidence of decreased pup (fetal) weight in these studies. Levels of DKP up to 2.4 percent of the diet were fed to the rat, equivalent to 2.4 g/kg body weight.

It should also be noted that a knowledge of experimental factors, such as the source and purity of DKP fed the animals, as well as the likelihood of effects that may be specific to the particular strain of rat used, is important in making meaningful comparisons of results from different laboratories. However, based on all the evidence available from reproductive studies, the agency concludes that pregnant women and their developing fetuses will not be harmed by exposure to DKP resulting from the decomposition of aspartame.

2. *Methanol.* One comment alleged that methanol, derived from the hydrolysis of the methyl ester in aspartame represents a serious health risk. The agency concludes that the level of dietary exposure to methanol is not of prime importance in the assessment of the safe use of aspartame. Methyl esters, which yield methanol on digestion, are not uncommon in foods. Dietary methanol also arises from fresh fruits and vegetables. It is estimated that a liter of beverage sweetened with aspartame would contain a maximum of 56 mg of methanol, if the aspartame were completely hydrolyzed. This is about one-third of the average methanol level that might be derived from a similar quantity of fruit juice. Clinical studies have shown that measurable blood levels of methanol are not detectable until single aspartame doses substantially exceed projected 99th percentile exposure levels (34 mg/kg) (Ref. 4). Thus, the agency finds no cause for concern from the levels of dietary methanol resulting from the highest projected levels of aspartame consumption.

3. *Other Reaction Products.* One comment questioned the safety of

aspartame for use in cooking on the grounds that all possible reaction products of aspartame and its derivatives have not been investigated for toxicity. Particular reference is made to possible nitrosamine derivatives of DKP or aspartame. The comment also argues that a more prominent label statement advising against cooking with aspartame is necessary.

FDA notes that Searle conducted a series of studies on potential nitrosation reactions as part of their original food additive petition (Ref. 5). These studies indicated that stable nitrosation products were not formed. The agency also concludes that the allegation that all possible reaction products have not been tested for safety is not a tenable issue in terms of regulatory food additive safety evaluation. Such a requirement for the demonstration of safety would necessitate an unlimited amount of experimental data. Scientific judgment is relied upon to identify potential areas of concern, such as the case with nitrosation products. Outside of these nitrosation derivatives, the agency has no basis for suspecting that potentially toxic derivatives could arise when aspartame is combined with food. Aspartame is structurally similar to a variety of natural dietary proteins which are customarily cooked and interact freely with other constituents of food.

It should also be noted that the current petition is solely for the use of aspartame in carbonated beverage, a use that is unlikely to result in aspartame being heated. In addition, the original approval attempts to avoid conditions under which aspartame would be used in cooking by limiting the types of products it can be used in and by requiring a label advisory not to use it for cooking or baking. The label statement, which is required on aspartame packaged for use as a sugar substitute and instructs that the product not be used in cooking or baking, is to inform users that the sweetener may not be efficacious for these uses. It is not a safety-related requirement. Certain label statements are necessary to ensure safe use, such as the warning to phenylketonurics (21 CFR 172.804(e)(2)). Other labeling provides information to aid in the efficacious use of the additive, as does the notice not to use aspartame in cooking or baking (21 CFR 172.804(e)(3)). This latter labeling requirement does not mean that all uses in cooking are without efficacy. It is impossible for a petitioner to explore all possible cooking combinations. The requirement does mean that the agency has concluded from the data available that the sweetener is not generally efficacious when used in foods exposed to high temperature cooking conditions. The agency, therefore, cannot agree that more prominent labeling to caution against cooking uses is warranted on the basis of safety concerns about harmful decomposition products.

C. Other Clinical Studies

To ensure further that the safety concerns expressed about potential adverse effects from additional exposure to aspartame are fully examined, the petitioner presented significant clinical studies on the use of aspartame in carbonated beverages. To assess the toxic potential of single high doses of aspartame, the substance was administered to patients in the fasting state so that peak plasma levels of amino acids would be accentuated. Doses given were up to 8 times greater than the highest estimated levels of daily intake resulting from all regulated food uses of aspartame plus its potential use in carbonated beverages. Combined blood levels of aspartic and glutamic acid did not exceed 10 micromoles/dL, a level far below that which results in acute hypothalamic lesioning in even the most sensitive animal species, the neonatal mouse (which requires about 60 micromoles/dL). Thus, even under extraordinary conditions of high aspartame ingestion over a short period of time (conditions which optimize peak plasma levels, but do not correspond to normal food intake which occurs throughout the daily waking period), the agency concludes that the plasma levels of aspartic acid, phenylalanine, and glutamic acid achieved do not indicate a potential for toxicity.

In addition to studies performed by Searle to evaluate the effects of acute administration of aspartame on plasma concentrations of free amino acids, the petitioner also monitored the influence of high continuous levels of aspartame on the day-to-day physiological processes of human subjects. In a study on long-term tolerance of aspartame on adults, doses as high as 135 mg/kg per day for 6 weeks resulted in no adverse clinical effects in a group of 50 adults. Ingestion by 126 children of 39.5 to 58.1 mg/kg per day (varying with age) of aspartame for 91 days showed no adverse clinical effect. Thus, regular ingestion of aspartame at dose levels far in excess of projected 99th percentile daily exposure (25 mg/kg) did not result in the occurrence of clinical anomalies or disorders.

Concern was also expressed by one comment about diabetic and geriatric populations that may be exposed to aspartame. The agency notes that the petitioner submitted the results of a clinical study performed on 39 insulin-dependent (14 male, 25 female) and 36 insulin-dependent (9 male, 27 female) diabetic subjects (ages 21 to 70 years). These subjects received 1.8 gm aspartame or (30 mg/kg) per day for 90 days. During the course of the study, no preexisting disease condition worsened, and neither aspartame nor placebo treatment produced changes or deterioration in the degree of diabetic control of any of the test subjects. Although none of the clinical studies performed were specifically directed at testing geriatric populations, the study in the diabetic population included elderly subjects. None of the subjects manifested any compound-related effects when administered up to 1.8 gm (30 mg/kg) per day of aspartame for 13 weeks.

Finally, the comments expressed concern about possible adverse affects of aspartame ingestion on other impaired individuals, such as individuals (e.g., alcoholic cirrhotics) whose liver function is severely compromised. Some clinicians believe that there is a relationship between the impaired ability to metabolize aromatic amino acids (e.g., phenylalanine) and the occurrence of a state of toxic encephalopathy. This toxic encephalopathy can lead in its extreme presentation to coma and even death. Patients with seriously impaired liver function would have their dietary intakes for all foods carefully monitored and controlled by a physician because of the high amino acid content in normal foods. The agency notes that the label on aspartame-containing products includes a statement which indicates phenylalanine content. If phenylalanine is a threat to these individuals, then the agency concludes that current labeling requirements should provide adequate warning.

IV. Environmental Findings

The agency has considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding may be seen in the Dockets Management Branch (address above), between 9 a.m. and 4 p.m., Monday through Friday.

V. Conclusions

FDA, having evaluated the data in the petition and other relevant material, concludes that the proposed food additive use is safe and that the

regulations should be amended as set forth below.

The administrative record shows that the regulatory approval is supported by more than 100 studies on the safety of aspartame and its decomposition products. These studies include an extensive program of clinical testing in various human subpopulations, as well as a complete series of toxicological tests in animals. All of these studies have been thoroughly reviewed by FDA scientists and the agency finds no basis upon which to alter the Commissioner's conclusions regarding the potential of aspartame to cause toxic effects, including brain tumors.

Further, the agency does not agree with the comments asserting that aspartame consumption beyond currently regulated uses will lower the margin of safety based on a toxic threshold of 100 micromoles/dL of combined aspartate and glutamate in blood, or that abnormal neurotransmitter activity might occur. Rather, the agency concludes that, because: (1) Ingestion of aspartame at high but conceivable amounts does not result in toxic plasma levels of amino acids, (2) these aspartame constituents are food-like and well-characterized with respect to metabolic fate and demonstrate no evidence of metabolic overload, and (3) clinically, no subpopulations, except homozygous PKU individuals or other individuals needing to control phenylalanine intake, have been identified that can suffer ill effects from long-term or excessive aspartame ingestion, the comments on the proposed addition of aspartame to carbonated beverages do not provide a basis for refusing to approve the petition.

In accordance with §171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Bureau of Foods (address above) by appointment with the information contact person listed above. As provided in 21 CFR 171.1(h)(2), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

VI. References

The following materials are on file in the Dockets Management Branch (address above) where they may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Fernstrom, J. D., M. H. Fernstrom, and M.A. Gillis, *Life Sciences*, 32:1651–1658, 1983.

2. Food Additive Master File 134, Study E32.

3. *Journal of Nutrition*, 109:768–717, 1979; *Journal of Nutrition*, 110:2216–2224, 1980; *Journal of Nutrition*, 109:2173–2181, 1979; *Journal of Toxicology and Environmental Health*, 7:291–305, 1981.

4. L. D. Stegink, et al., *Journal of Toxicology and Environmental Health*, 7:281–290, 1981.

5. Food Additive Master File 134, Studies E50, E68, and E71.

List of Subjects in 21 CFR Part 172

Food additives, Food preservatives, Spices and flavorings.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 72 Stat. 1784–1788 as amended (21 U.S.C. 321(s), 348)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), Part 172 is amended in § 172.804 by adding new paragraph (c)(6) to read as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

§ 172.804 Aspartame.

* * * * *

(c) * * *

(6) Carbonated beverages and carbonated beverage syrup bases.

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Any person who will be adversely affected by the foregoing regulation may at any time on or before August 8, 1983, submit to the Dockets Management Branch (address above) written objections thereto and may make a written request for a public hearing on the stated objections. Each objection shall be separately numbered and each numbered objection shall specify with particularity the provision of the regulation to which objection is made. Each numbered objection on which a hearing is requested shall specifically so state; failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held; failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this regulation. Received objections may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Effective date. This regulation shall become effective July 8, 1983.

(Secs. 201(s), 409, 72 Stat. 1784–1788, as amended (21 U.S.C. 321(s), 348))

Dated: June 29, 1983.

Mark Novitch,

Acting Commissioner of Food and Drugs.

[FR Doc. 83-18193 Filed 7-1-83; 11:49 am]

BILLING CODE 4160-01-M

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21 CFR Parts 175 and 178

[Docket No. 83F-0042]

Indirect Food Additives: Adhesive Coatings and Components; Adjuvants, Production Aids, and Sanitizers

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of 2,2'-ethylidenebis(4,6-di-*tert*-butylphenol) as a component of adhesives and as an antioxidant and/or stabilizer in acrylonitrile-butadiene-styrene copolymers and rubber-modified (high impact) polystyrene. This action responds to a petition filed by Schenectady Chemicals, Inc.

DATES: Effective July 8, 1983; objections by August 8, 1983.

ADDRESS: Written objections to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Vir Anand, Bureau of Foods (HFF–334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–472–5690.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of March 4, 1983 (48 FR 9376), FDA announced that a petition (FAP 3B3691) had been filed by Schenectady Chemicals, Inc., P.O. Box 1046, Schenectady, NY 12301, proposing that the food additive regulations be amended to provide for the safe use of 2,2'-ethylidenebis (4,6-di-*tert*-butylphenol) as a component of adhesives and as an antioxidant and/or stabilizer in acrylonitrile-butadiene-styrene copolymers and rubber-modified (high impact) polystyrene.

FDA has evaluated data in the petition and other relevant material and concludes that the proposed food additive use is safe and that the regulations should be amended as set forth below.

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the